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TITLE: Phase I/II Trial of 13-Cis Retinoic Acid, Alpha Interferon, Taxotere, and Estramustine (R.I.T.E.) for the Treatment of Hormone Refractory Prostate Cancer

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14. ABSTRACT

Advanced prostate cancer is only temporarily controlled with androgen ablation therapy. In order to overcome tumor resistance, we developed a epithelial cell line model to dissect out important mechanisms of resistance such as mutations in p53 and *bcl-2* overexpression. In an attempt to sensitize these cells to paclitaxel (TAX), we found that 13-cis retinoic acid and alpha interferon (CRA/IFN) was capable of overcoming bcl-2 mediated resistance and reduced the expression of bcl-2 in human prostate cancer cells. We hypothesized that drugs, which could overcome bcl-2 mediated resistance, would improve chemotherapy response or duration of response in the clinic. We then translated these results to the clinic in a series of clinical trials. Recently, our phase II study with CRA/IFN/TAX was accepted as a National trial and is ongoing in the Eastern Cooperative Oncology Group. Given recent studies demonstrating that the combination of estramustine and docetaxel (ET) has increased response against HRPC in the clinic, but limited median duration of response, and our studies of CRA/IFN in the laboratory and clinic, we hypothesized that CRA/IFN will improve the response rate, or duration of response, of ET in patients with HRPC. We will treat patients with HRPC with R.I.T.E. therapy in a phase I and II trial.

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INTRODUCTION:

Advanced prostate cancer is only temporarily controlled with androgen ablation therapy. The use of chemotherapy is also limited with a median duration of response of only 5-6 months in all known regimens, secondary to the genomic instability of prostate cancer and subsequent development of tumor resistance. For example, one of the most active, and most utilized, combinations against HRPC is estramustine and taxotere with a 60% response rate, but a median duration or response of only 6 months. In order to overcome tumor resistance, we developed a pre-clinical epithelial cell line model to dissect out important mechanisms of resistance such as mutations in p53 and *bcl-2* overexpression, which increase with progression of tumors and development of resistance. This model was derived from primary baby rat kidney epithelial cells (BRK) transfected with genes encoding the murine temperature sensitive p53(val135) and a *bcl-2* expression vector. In an attempt to sensitize these cells to paclitaxel (TAX), we found that 13-cis retinoic acid and alpha interferon (CRA/IFN) was capable of overcoming bcl-2 mediated resistance and reduced the expression of bcl-2 in human prostate cancer cells. We hypothesized that drugs, which could overcome bcl-2 mediated resistance, would improve chemotherapy response or duration of response in the clinic. We then translated these results to the clinic in a series of clinical trials. In a pilot clinical trial using CRA/IFN alone in patients with prostate cancer, we demonstrated safety and activity in some patients. In a phase I trial, CRA/IFN in combination with TAX was well tolerated, had clinical activity, and reduced bcl-2 expression in peripheral blood mononuclear cells (PBMCs), which we studied as a potential biological marker of drug effect. Recently, our phase II study with CRA/IFN/TAX was accepted as a National trial and is ongoing in the Eastern Cooperative Oncology Group. Additional laboratory studies demonstrated that CRA/IFN decreased cell viability with regimens more commonly used for HRPC including estramustine/taxotere. Given recent studies demonstrating that the combination of estramustine and taxotere (ET) has increased response against HRPC in the clinic, but limited median duration of response, and our studies of CRA/IFN in the laboratory and clinic, we hypothesized that CRA/IFN will improve the response rate, or duration of response, of ET in patients with HRPC. We will treat patients with HRPC with R.I.T.E. therapy in a phase I and II trial. We will assess bcl-2 expression as a biological marker of effect in PBMCs and in tumor in patients.

Our specific aims are:

1. To conduct phase I/II trial of CRA/IFN with taxotere and estramustine (R.I.T.E) in patients with HRPC to determine the maximal tolerated dose, clinical response, and duration of response.
2. To determine the effect of R.I.T.E therapy on bcl-2 in PBMCs and tumor.

BODY:

Based on our prior data, as noted above, we hypothesized that CRA/IFN will improve the response rate, or duration of response, of ET in patients with HRPC, and developed a phase I and II study. Although this report covers the period of 2/15/03 to 2/14/04, the project was delayed in starting secondary to required approvals and revisions of the clinical trial. As requested, we submitted the clinical trial to the Surgeon General's Human Subjects Research Review Board (HSRRB) and obtained approval on 10/7/2002. Following the approval, the approved version of the trial and consent was submitted to our IRB and required amendment, which was approved 1/3/03. Personnel were hired and the trial opened to accrual 3/03. We have now reached our dose limiting toxicity (fatigue) in two patients in cohort 4 and will complete the phase I part of the study when an additional 3 patients are enrolled in cohort 3. Currently, 29 patients have now been enrolled on the phase I/II study. 16 patients were enrolled to fully complete the phase I portion of the study, and the phase II dose was identified. PBMCs were collected at baseline and day 2-4 for assessment of Bcl-2 expression. To date, we conclude that RITE therapy is well tolerated and active and the phase II study is ongoing. An abstract of data for the study has published in American Society of Clinical Oncology proceedings (PASCO 2005, abstract 4740). The timeline is as follows:

Task 1: To determine the safety and maximal tolerated dose of R.I.T.E. therapy.

- **A. Treat patients with R.I.T.E. with dose escalations to determine the MTD (Completed).**
- **B. Begin to assess peripheral blood and tumor when available for bcl-2, bclXL, bax and other apoptotic proteins by Western analysis (Completed).**

Task 2: To determine the response rate and duration of response of the regimen R.I.T.E. in HRPC.

- **A. Complete phase II portion of the trial based on the dose obtained in the phase I portion of the trial, with assessment of PSA and tumor response (Ongoing).**
- **B. Assess response after the first 14 patients to determine if this regimen is active. (Ongoing).**

Task 3: Assess PBMCs and tumor for bcl-2.

- **A. Perform Western analysis on tumor and PBMCs for bcl-2 and other apoptotic proteins (Years 2-4).**
- **B. Make preliminary analysis on possible correlations in effect on PBMCs and response with Dr. Shih.**
- **C. Assess response and duration with Dr. Shih to determine the number of patients needed to complete future phase III trials comparing RITE with TE (Year 4).**

KEY RESEARCH ACCOMPLISHMENTS

Full approval of the phase I and II clinical trial

Completion of phase I part of the study and publication of abstract to the American Society of Clinical Oncology, 2005.

Ongoing phase II study

REPORTABLE OUTCOMES:

PASCO 2005 abstract, as noted above.

CONCLUSIONS:

As planned, we have obtained approval and initiated the clinical study, with completion of the phase I part of the study. 29 total patients have been enrolled on the phase I/II study. 16 patients have completed the phase I portion and 13 patients enrolled on the phase II portion. patients have been accrued to Phase II of this study. The timeline initially changed, as noted in the report dated 3/13/03, given time required for study approval and need for further accrual. Ongoing accrual of the phase II study will continue with extension to 2/14/2007.